34. The method of claim 26, wherein the contacted cell expresses HVEM and the composition is a soluble p30 polypeptide.

35. The method of claim 26, wherein the contacted cell expresses LTβR and the composition is a soluble p30 polypeptide.

36. The method of claim 26, wherein the contacted cell expresses p30 polypeptide on its cell surface and the composition is a soluble HVEM polypeptide.

Please add the following new claims:

--51. (New) The method of claim 26, wherein the composition that binds to a p30 polypeptide, HVEM or LTβR is an antibody; a fusion protein comprising p30 polypeptide, HVEM or LTβR; or a functional fragment of p30 polypeptide, HVEM or LTβR.

52. (New) The method of claim 26, wherein the composition that binds to a p30 polypeptide, HVEM or LTβR is selected from soluble HSV gD-1, gD-1 (Δ290-299t), HVEM:Fc, LTβR:Fc, or LIGHT-t66.--

REMARKS

These remarks are in response to the Office Action mailed March 12, 2002. Claims 1 to 50 are pending. Claims 1 to 25, 33 and 37 to 50 stand withdrawn from examination as directed to a non-elected invention. New claims 51 and 52, which depend from claim 26, have been added. Accordingly, upon entry of the amendment, claims 26 to 32, 34 to 36, 51 and 52 are under consideration.

Regarding the Amendments to the Specification

The specification has been amended to address various informalities. In particular, the relationship between the subject application and related applications is more clearly indicated. Sequence identifiers (SEQ ID NOS:7-16) have also been inserted as indicated above to refer to nucleic acid sequences as required by 37 C.F.R. §1.821-1.825. Substitute paper and computer readable copies of the Sequence Listing with additional SEQ ID NOS:7-16 in accordance with 37 C.F.R. §1.825 are also submitted herewith. An executed statement under 37 C.F.R. §1.821(f) and (g) indicating that the Substitute paper and computer readable copies of the Sequence Listing are the same and do not add new matter is submitted concurrently herewith. Accordingly, as the

amendments to the specification and the Substitute Sequence Listing do not add new matter, entry thereof is respectfully requested.

Regarding the Amendments to the Claims

Support for the amendments to claim 26 can be found throughout the specification. In particular, the amendment to claim 26 to recite that the composition "binds to a p30 polypeptide, HVEM or LTβR" is supported, for example, at page 18, lines 14-20; page 19, lines 23-24; page 23, lines 1-3; page 30, lines 6-7; page 40, lines 3-10; and at page 41, lines 16-25, which discloses compositions that bind to p30 polypeptide, HVEM and LTβR. The amendment to claim 26 to recite that the p30 polypeptide has "an apparent molecular weight of about 30kDa as determined by SDS-PAGE and an isoelectric charge (pI) of between about pI 7 to about pI 8.5 and that binds HVEM or LTβR" is supported, for example, at page 17, lines 18-23. The amendment to claim 26 to substitute the term "a" for "an" was made to address an informality. Accordingly, as the amendments to claim 26 are supported by the specification or were made to address an informality, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claims

Support for new claims 51 and 52, directed to compositions that bind to a p30 polypeptide, HVEM or LTβR, including an antibody, a fusion protein comprising p30 polypeptide, HVEM or LTβR, a functional fragment of p30 polypeptide, HVEM or LTβR, soluble HSV gD-1, gD-1 (Δ290-299t), HVEM:Fc, LTβR:Fc, or LIGHT-t66, can be found throughout the specification. In particular, claims 51 and 52 are supported by originally filed claim 26. Claims 51 and 52 are also supported at page 17, lines 27-29; page 18, lines 14-18 and lines 29-30; page 20, lines 22-29; page 23, lines 1-10; and page 30, lines 6-14. Accordingly, as claims 51 and 52 are supported by the specification no new matter has been added and entry thereof is respectfully requested.

Applicants respectfully request reconsideration of the present application.

I. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 26 to 32 and 34 to 36 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. The Examiner indicates allegedly that

"the specification does not teach how to make and use any composition for a method of inhibiting any p30 polypeptide-mediated cellular response wherein the response modulate any autoimmune disease such as the ones recited in claim 32."

The specification enables the claims as originally filed. In any event, the claims have been amended as set forth above. The rejection will therefore be addressed in respect to the amended claims.

Claim 26, as amended, is directed to a method for inhibiting a p30 polypeptide-mediated cellular response including 1) providing a composition that binds to a p30 polypeptide, HVEM or LTβR and that inhibits binding of a cell surface expressed p30 polypeptide to a cell surface expressed HVEM or LTβR, said p30 polypeptide having an apparent molecular weight of about 30kDa as determined by SDS-PAGE and an isoelectric charge (pI) of between about pI 7 to about pI 8.5 and that binds HVEM or LTβR; and 2) contacting the cell expressing the cell surface expressed p30 polypeptide or the cell surface expressed HVEM or LTβR with an amount of the composition sufficient to inhibit a p30 polypeptide-mediated cellular response. In respect to compositions that may be used to practice the claimed method, amended claim 26 requires 1) that the composition "binds to a p30 polypeptide, HVEM or LTβR" and 2) that the composition "inhibits binding of a cell surface expressed p30 polypeptide to a cell surface expressed HVEM or LTβR." Accordingly, the composition has two recited functions and, therefore, contrary to the Patent Office's position, is not "any composition."

In addition to the compositions having defined functions, the specification teaches how to identify compositions having the recited functions for practicing the claimed methods. For example, the specification teaches competition binding assays for identifying compositions that inhibit binding of HVEM and LT (see, for example, Example 2, pages 49-50 and Example 4, pages 52-53). In particular, Example 2 describes flow cytometric assays that can be used to identify competitive inhibitors of a binding reaction, irrespective of whether the inhibitors share any structural similarity. The specification also teaches *in vivo* and other assays for characterizing the activity of the identified compositions that inhibit binding (see, for example, Example 7, page 56; Example 8, pages 56-57; Example 9, pages 57-58; and Example 13, pages 64-57). In addition, Example 10 describes a functional assay for competition binding: LIGHT t66 induces cell death of HT29 cells and, therefore, inhibitors of LIGHT binding to LTβR:Fc can be identified as those that inhibit HT29 cell death (page 59). Furthermore, other assays for

identifying inhibitors of binding are well known in the art including, for example, ELISA. Thus, in view of the guidance in the specification and knowledge in the art, one skilled in the art could readily identify compositions having the requisite functions for use in the claimed methods without undue experimentation.

Moreover, the specification exemplifies four different compositions, soluble HSV gD-1, gD-1 (Δ290-299t), HVEM:Fc, LTβR:Fc, and LIGHT-t66, having the requisite functions. In addition to these four exemplified species, the specification teaches how to produce fragments, variants, mimetics, fusions and other forms of these species (see, for example, page 20, line 22, to page 23, line 25). Furthermore, the specification teaches how to produce antibodies, including chimeric antibodies, single chain, and fragments thereof, having the recited functions (see, for example, page 30, line 6 to page 32, line 21). Thus, in view of the guidance in the specification, one skilled in the art could readily make additional compositions based on the four exemplified species having the recited functions.

Thus, given that the specification teaches the skilled artisan in vitro, cell based and *in vivo* assays for identifying compositions having the recited functions, exemplifies four different compositions having the recited functions and, furthermore, teaches how to produce variants of the four exemplified species and antibodies that bind to the four exemplified species, undue experimentation would not be required to produce the recited compositions. As such, it cannot objectively be stated that there is insufficient guidance for identifying and producing a genus of compositions having the recited functions.

In respect to the recited p30 polypeptide, amended claim 26 requires that the p30 polypeptide 1) have "an apparent molecular weight of about 30kDa as determined by SDS-PAGE;" 2) have "an isoelectric charge (pI) of between about pI 7 to about pI 8.5;" and 3) "binds HVEM or LTβR." Accordingly, the p30 polypeptide of claim 26 has defined physical, chemical and functional characteristics and, therefore, contrary to the Patent Office's position, is not "a p30 polypeptide having no structure associated with function."

In respect to claim 32 and the recited autoimmune diseases, more particularly the Patent Office's position that allegedly there is insufficient guidance for treating "any autoimmune disease," Applicants respectfully point out that the claims are not directed to treating "any" autoimmune disease. Rather, claim 26 is directed to inhibiting a p30 polypeptide-mediated

cellular response. Thus, the lymphoma, leukemia and autoimmune disease recited in depending claims 31 and 32 are mediated, at least in part, by a p30 polypeptide-mediated cellular response.

Further in respect to the claim 32 and the recited autoimmune diseases, both of the Van Noort *et al.* and Tian *et al.* references cited by the Patent Office do not support a lack of enablement of the claimed methods. Specifically, the Tian *et al.* reference discusses antigen-based immunotherapy for treating autoimmune disease (see, for example, Tian *et al.* at page 190, column 2; page 192, paragraph bridging columns 1 and 2; page 193, column 1, second paragraph; and page 194, column 1, first full paragraph). In contrast, the claimed methods relate to cytokine based therapy, which does not depend on the initiating antigen. Accordingly, Tian *et al.* is irrelevant as to enablement of the claimed methods.

The Van Noort *et al.* reference is a lengthy review article discussing autoimmunity, which includes an overview of causes and potential therapies for treating autoimmune disease. Van Noort *et al.* describe difficulties associated with autoantigen identification and using specific antigens or antigen analogs to reestablish tolerance towards them (see, for example, page 182-188). However, Van Noort *et al.* do not suggest that cytokine based methods of autoimmune disease treatment will be unsuccessful, let alone the claimed methods. At most, Van Noort *et al.* describe cytokine modulation of autoimmune response, indicating that the results for cytokine therapy are varied, sometimes promising, other times inconclusive (see, for example, page 188-191). However, taken as a whole, the Van Noort *et al.* reference cannot fairly be said to support a lack of enablement of cytokine based therapies in general, let alone the specifically claimed methods. Thus, Van Noort *et al.* fail to support an alleged lack of enablement of the claimed methods.

In sum, the Tian *et al.* reference is irrelevant to the claimed methods, and the Van Noort *et al.* reference taken as a whole cannot objectively be said to support a lack of enablement of the claimed methods. Accordingly, the cited Tian *et al.* and Van Noort *et al.* references fail to support this grounds for rejection.

In support of enablement of the claimed methods, as acknowledged by the Examiner, the specification discloses, *inter alia*, 1) HVEM:Fc inhibition of delayed type hypersensitivity and 2) HVEM:Fc reduction of inflammation in a collagen induced arthritis animal model. Furthermore, that the claimed methods are applicable to different autoimmune diseases is corroborated by Exhibit A, a publication by Tamada *et al.* (J. Clin. Invest. 109:549 (2002)) and Exhibit B, a

second publication by Tamada *et al.* (Nature Med. 6:283 (2000), submitted herewith. In Exhibit A, the authors state that "blockade of LIGHT, a T cell costimulatory molecule belonging to the TNF superfamily, by soluble lymphotoxin β receptor-Ig (LT β R-Ig) inhibits the cytotoxic T lymphocyte (CTL) response to host genetic disparities and ameliorates lethal graft-versus-host disease (GVHD)." (see abstract, first line) In Exhibit B, the authors state that "blockade of LIGHT by administration of soluble receptor or antibody led to decreased cell-mediated immunity and ameliorated graft-versus-host disease." (see abstract, second to last line) Thus, in view of the fact that the specification discloses that delayed type hypersensitivity and inflammation in a collagen induced arthritis animal can be inhibited as claimed, and further in view of Exhibits A and B, which indicate that blockade of LIGHT by receptor or antibody ameliorates graft-versus-host disease, the claimed methods are applicable to different autoimmune diseases and, therefore, are enabled as claimed.

In sum, in view of the guidance in the specification which teaches how to identify and produce compositions for practicing the claimed methods, that the recited p30 polypeptide is defined chemically, physically and functionally, and that the claimed methods are applicable to different autoimmune diseases, as corroborated by Exhibits A and B, the claims are adequately enabled. Accordingly, Applicants respectfully request that the grounds for rejection under 35 U.S.C. §112, first paragraph, for enablement be withdrawn.

The rejection of claims 26 to 32 and 34 to 36 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. The Examiner indicates that "the specification discloses only three compositions....consisting of .... HSV gD-1 protein, LIGHT t66, and HVEM:Fc chimeric protein for a method of inhibiting a p30 polypeptide of SEQ ID NO:6" and allegedly that "with the exception of the specific polypeptides....there is insufficient written description about the structure associated with functions of any soluble p30 polypeptide,. Any soluble HVEM polypeptide as a composition for a method for inhibiting p30 polypeptide mediated cellular response such as inhibited lymphocyte proliferation in rheumatoid arthritis." The Examiner therefore alleges that "the disclosure fails to provide a representative number of species to describe the genus." [see Office Action, page 7, second paragraph through page 8, first paragraph]

The specification provides an adequate written description of the claimed subject matter. In any event, the claims have been amended as set forth above and the rejection will therefore be addressed in respect to the amended claims.

To satisfy the written description requirement, the specification must apprise the skilled artisan of the invention in sufficient detail to demonstrate Applicants had possession of the invention. Possession may be shown by "any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000).

In the present case, the recited compositions of the claimed methods must: bind to a p30 polypeptide, HVEM or LTβR and inhibit binding of a cell surface expressed p30 polypeptide to a cell surface expressed HVEM or LTβR. Thus, the compositions are defined functionally.

As to structural features, as discussed above, the specification exemplifies four species having the requisite functions, soluble HSV gD-1, gD-1 (Δ290-299t), HVEM:Fc, LTβR:Fc, and LIGHT-t66. As to a structural relationship among the four species, HSV gD-1 and gD-1 (Δ290-299t) are clearly related by sequence. Furthermore, HVEM and LTβR are both members of the TNFR superfamily which have common sequence motifs. Moreover, HVEM:Fc and LTβR:Fc both bind to p30 polypeptide. Since both HVEM:Fc and LTβR:Fc bind to p30 polypeptide there may be a structure inherently present within the proteins that mediates the binding. Thus, there are structural features in common among the four exemplified species.

In addition to the common structural features among the four exemplified species, the recited compositions will have inherent structures because they all bind to a p30 polypeptide, HVEM or LTβR. That is, each of HSV gD-1, gD-1 (Δ290-299t), HVEM:Fc, LTβR:Fc, and LIGHT-t66 or any other composition will have a structure that: 1) binds to a p30 polypeptide, HVEM or LTβR; and 2) inhibits binding of a cell surface expressed p30 polypeptide to a cell surface expressed HVEM or LTβR. Thus, although different compositions are applicable in the invention, any structure that mediates binding to a p30 polypeptide, HVEM or LTβR is inherently present in the composition and is limited in number because it must bind to a p30 polypeptide, HVEM or LTβR and inhibit binding of a cell surface expressed p30 polypeptide to a cell surface expressed HVEM or LTβR. Accordingly, such structures are conserved in

number. Further in this regard, no Applicant has ever been refused a patent because Applicant did not exhaustively determine every structure capable of binding to a particular molecule and identify features common among all of the structures. This is particularly relevant in the present case given that the composition need only bind to one of the three different molecules, p30 polypeptide, HVEM or LTβR and that the courts have repeatedly stated that "an Applicant need not disclose every species encompassed by a claim." See, e.g., *In re Angstadt*, 537 F.2d 498 (C.C.P.A. 1976)

Finally, in addition to the four exemplified species, as also discussed above the specification teaches peptide fragments, variants, mimetics, fusions of the particular species (see, for example, page 20, line 22, to page 23, line 25), as well as antibodies, including chimeric antibodies, single chain, and fragments thereof, having the requisite functions (see, for example, page 30, line 6 to page 32, line 21). The skilled artisan readily recognizes the nature of these various compositions based upon HSV gD-1, gD-1 (Δ290-299t), HVEM:Fc, LTβR:Fc, and LIGHT-t66 and, as such, would be apprised of Applicant's invention.

In sum, as the recited compositions applicable in the methods of the invention are defined functionally, share a structure inherently or otherwise, and, furthermore, that the specification exemplified four species and teaches various forms of the species and antibodies having the requisite functions, sufficient relevant identifying characteristics of the compositions are provided. As such, the skilled artisan would be apprised of Applicants invention and the rejection under 35 U.S.C. §112, first paragraph for lacking an adequate written description should properly be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 26 to 32, 34 to 36, 51 and 52 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 03-3975.

Respectfully submitted,

Date: 9/12/02

John R. Wetherell, Jr. , Ph.D.
Reg. No. 31,678

associated 30 kDa HVEM ligand may function as a proliferation-inducing signal for T cells.

LTα has previously been shown to stimulate growth enhancing activities for B lymphocytes, including Epstein-Barr virus transformed cell lines (Abken (1992) J. Immunol. 149:2785; Estrov (1993) J. Exp. Med. 177:76; Kehrl (1987) Science 238:1144; Gibbons (1994) Eur. J. Immunol. 24:1879). HVEM is also expressed on B lymphoblastoid lines (Figure 7A). Anti-HVEM antibody, when added to cultures of RAJI B cell lines in medium with 2% serum, stimulated the uptake of 3H-thymidine in a dose-dependent fashion, indicating that HVEM can signal maintenance of B cell viability in low serum (Figure 7B). LTα exhibited a 2 to 3 fold stimulatory effect in this assay. The presence of TNFR60 and TNFR80 as negative growth factors may contribute a low response to LTα. The positive effect of anti-HVEM antibody may be a property unique to p30 (HVEM-ligand, LIGHT).

Example 6: Production of mouse HVEM:Fc

This example demonstrates the construction of a mouse HVEM:Fc recombinant construct.

The extracellular region of mouse HVEM was amplified by PCR from the mHVEM cDNA (Hsu *et al.*, 1997) starting with Met1 and ending at Ser205 (forward primer= 5'- tatGGATTCatggaacctctcccaggat-3', and reverse primer= 5'-tatGGATTCggaggagcaggt ggtgtctgt-3'; both primers contain a BamHI site (SEQ ID NOS: 7-8). The 550 bpPCR product was purified by Wizard PCR Preps (Promega), digested with BamHI and then ligated in-frame into BglII cut Baculovirus vector pVL1392 (Pharmingen) containing the Fc region of human IgC1 at the 3' end of the HVEM insert (pVL1392-mHVEM:Fc). The ligation reaction mixture was used to transform XL-1 blue competent cells (Stratagene) for a plasmid preparation.

TN5 insect cells ($1.25x10^6$) were plated on a T25 flask in 4 mL Excell 401 Medium (JRH Biosciences) and allowed to attach for 2 hours. TN5 cells were co-transfected with 1μg pVL1392-HVEMFc plasmid and 250 ng Baculogold™ DNA (Pharmingen) using 14μg Lipofectin™ (Gibco BRL). The following day the medium was exchanged and the supernatant containing virus was collected after 4 days. The virus was amplified to make a stock for protein production.

affinity chromatography on a column of monoclonal anti-FLAG (M2) coupled to Affigel™ (Biorad). LIGHT t66 was eluted from the column using 20mM glycine, 150 mM NaCl, pH 3.0, and neutralized immediately by collection into 50 mM Tris pH 7.4.

A soluble form of LIGHT (LIGHT t66) with the addition of an N-terminal FLAG epitope was produced in stably transfected 293 cells and purified to homogeneity by ion exchange followed by immuno-affinity purification on an affinity matrix of monoclonal anti-FLAG (M2). Final yield of the protein was 80%and purity >95% (Figure15A).

Primer-introduced sequence modification was used to generate soluble LIGHT with the following single amino acid substitutions: G119E, L120Q Q11TT, and Y173F. Briefly, internal primers were designed to introduce a restriction site at the mutation location. Forward and reverse primers containing the mutations were used in separate PCR reactions to amplify two regions of soluble LIGHT. Primers (SEQ ID NOS: 9-16) were as follows:

Q117T :	5' ACGCTGGGCCTGGCCTXCTGA_3',
	5' ACTCTCCCATAACAGCGGCC_3'.
G119E:	5' GAGCTGGCC_ITGCTGAGGGGCCT_3",
	5'_CAGCTGAGTCTCCCATAACA_3'.
L120Q:	5' CAGGCC_ITCCTGAGGGGCCTCA_3
	5' GCCCAGCTGAGTCTCCCATAA_3'.
Y 173F:	5' TTCCCCGAGGAGCTGGAGCT_3
	5'_GCGGGGTGTGCGCTTGTAGA_3'.

The PCR products were ligated at the primer-introduced restriction enzyme site to create soluble LIGHT starting at amino acid t66 and containing one of the 4 amino acid substitutions. The LIGHT t66 mutants were ligated into the FLAG-tagged cassette, pBABE-FLAG which contains the V-cam signal sequence fused to the FLAG epitope. The V-cam FLAG-LIGHT mutant inserts were cloned into pCDNA3.1 (+) (Invitrogen). All mutants were sequenced (ABI310 automated sequencer) for unambiguous verification. For protein production, 293T cells (1.5 x 10^6 cells/10 cm dish) were transfected with 5 pg DNA. Medium containing soluble protein was collected after 24 h in culture.

LIGHTt66-FLAG mutants were purified from 24 h culture supernatant in a one step immunoaffinity procedure using an affinity matrix of monoclonal anti- FLAG antibody (M2) coupled to Affigel™ (5 mg antibody per ml of gel). Culture supernatant (50

CLEAN COPY OF CLAIMS

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26. A method for inhibiting a p30 polypeptide-mediated cellular response comprising

(a) providing a composition that binds to a p30 polypeptide, HVEM or LTβR and that inhibits binding of a cell surface expressed p30 polypeptide to a cell surface expressed HVEM or LTβR, said p30 polypeptide having an apparent molecular weight of about 30kDa as determined by SDS-PAGE and an isoelectric charge (pI) of between about pI 7 to about pI 8.5 and that binds HVEM or LTβR; and

(b) contacting the cell expressing the cell surface expressed p30 polypeptide or the cell surface expressed HVEM or LTβR with an amount of the composition sufficient to inhibit a p30 polypeptide-mediated cellular response.

27. The method of claim 26, wherein the cell is contacted with the composition *in vivo*.

28. The method of claim 26, wherein the inhibited p30 polypeptide-mediated cellular response comprises inhibition of a lymphocyte cellular response.

29. The method of claim 28, wherein the inhibited lymphocyte response is lymphocyte proliferation.

30. The method of claim 28, wherein the inhibited lymphocyte is a pathogenic effector cell.

31. The method of claim 28, wherein the inhibited lymphocyte response modulates a T or a B lymphoma or leukemia or an autoimmune disease.

32. The method of claim 31, wherein the autoimmune disease is rheumatoid arthritis, insulin-dependent diabetes mellitus, multiple sclerosis, systemic lupus erythematosus or myasthenia gravis.

34. The method of claim 26, wherein the contacted cell expresses HVEM and the composition is a soluble p30 polypeptide.

35. The method of claim 26, wherein the contacted cell expresses LTβR and the composition is a soluble p30 polypeptide.

36. The method of claim 26, wherein the contacted cell expresses p30 polypeptide on its cell surface and the composition is a soluble HVEM polypeptide.

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51. The method of claim 26, wherein the composition that binds to a p30 polypeptide, HVEM or LTβR is an antibody; a fusion protein comprising p30 polypeptide, HVEM or LTβR; or a functional fragment of p30 polypeptide, HVEM or LTβR.

52. The method of claim 26, wherein the composition that binds to a p30 polypeptide, HVEM or LTβR is selected from soluble HSV gD-1, gD-1 (Δ290-299t), HVEM:Fc, LTβR:Fc, or LIGHT-t66.

CLEAN COPY OF SPECIFICATION PAGES 1, 55, and 62

LIGAND FOR HERPES SIMPLEX VIRUS ENTRY MEDIATOR AND METHODS OF USE[0]

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Serial No. (USSN) 09/524,325, filed March 13, 2000, which is a divisional of USSN 08/898,234, filed July 30, 1997 (now U.S. Patent No. 6,140,467), which are incorporated herein by reference in its entirety for all purposes and to which application a priority claim is made under 35 U.S.C. §120.

STATEMENT AS TO FEDERALLY-SPONSORED RESEARCH

The United States Government has certain rights in this invention pursuant to grant nos. AI33068 and CA69381 awarded by National Institutes of Health (NIH), DHHS.

FIELD OF THE INVENTION

The invention relates generally to compounds and methods useful in regulating immune responses and viral infection.

BACKGROUND OF THE INVENTION

Herpes simplex virus (HSV), types 1 and 2, causes recurrent infections that range in severity from benign to serious. HSV emerges from latency in neurons to infect the skin and other tissues in the presence of a competent cellular immune system. The D glycoprotein (gD) of HSV, a transmembrane protein located in the virion envelope, initiates infection by binding to cellular receptors (Spear *et al.* (1993) Viral Fusion Mechanisms. Ed. Bentz. CRC press, Boca Raton). Recently, a cellular protein used by HSV for infection was identified and given the term HSV entry mediator (HVEM) (Montgomery (1996) Cell 87:427). HVEM is a transmembrane type 1 protein with a cysteine-rich extracellular domain that exhibits significant homology with receptors for tumor necrosis factor (TNF)-related cytokines (Smith *et al.* (1994) Cell 76:959; Ware *et al.* (1995) in, Pathways of Cytolysis. Eds. Griffiths and Tschopp. Springer-Verlag, Basel). Many of the TNF superfamily members initiate a variety of cellular responses necessary to mount effective inflammatory and immune responses.